

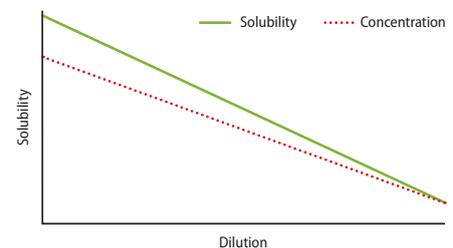


# SUCCESSFUL PARENTERAL FORMULATIONS BY PREVENTING CRYSTALLIZATION

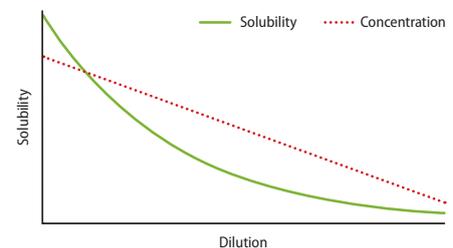
Many drug substances are formulated as parenteral formulations and administered directly into the systemic circulation in animals and humans. In order to improve their stability and solubility, many parenteral formulations are formulated using a co-solvent. Ampule or vial dosage forms are often co-solvent concentrated formulations. These concentrates are finally diluted before administered to the patient. Nevertheless, there are many cases known where dilution of drug formulations has the potential to generate conditions where drug concentrations are supersaturated. Under these circumstances, drug precipitation/crystallization is likely to take place. Drug precipitation after parenteral administration may cause mechanical or chemical irritation at the injection site, and potentially even more serious systemic effects.

The main challenge is that the solubility of an active ingredient in a mixture of solvents may not be linear during dilution. The sooner the temperature dependent solubility of the active ingredient is determined, the better.

Simple **Crystal16** solubility measurements help avoid vulnerable formulations and foresee mechanical and chemical irritation at injection site. Additionally the particle visualization module of the **Crystalline** instrument can provide in situ information about the crystallization behavior of a compound and the stability of a final formulation.



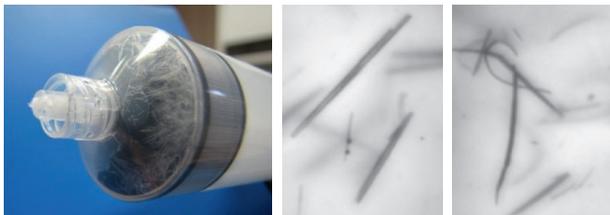
*Solubilized formulation/no crystallization*



*Supersaturated formulation/crystallization may occur*

## CASE STUDY: Avoiding crystallization of lorazepam during infusion

Lorazepam is a strong sedative for intensive care patients and a commonly used method of administering it to the patient is by infusion of a freshly prepared lorazepam solution. During lorazepam infusion, unwanted lorazepam crystallization occurs, resulting in line obstruction and reduced lorazepam concentrations.



Lorazepam crystallization during dilution in a syringe

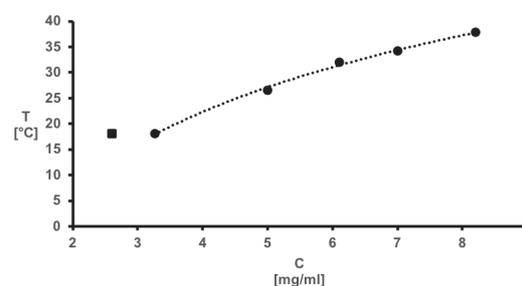
The commercial lorazepam solution is quite viscous and therefore dilutions with aqueous NaCl solution or 5% glucose are always prepared before injection. Nevertheless, upon administering lorazepam, obstruction of the infusion lines or syringe occurs frequently. Experiments to visualize the crystallization process of lorazepam were carried out in the **Crystalline** multiple reactor setup. Known volumes of the commercially available lorazepam solution and the aqueous glucose solution were added to prepare lorazepam solutions with known overall composition. The crystallization process of lorazepam could be followed in-situ with the help of the **Crystalline** particle visualization module.

ter Horst *et al* observed that lorazepam crystals exhibit an extremely needle-like morphology when formed at or below a concentration of 0.5 mg/ml. Interestingly, at higher concentrations the needles were deformed and strongly curled.

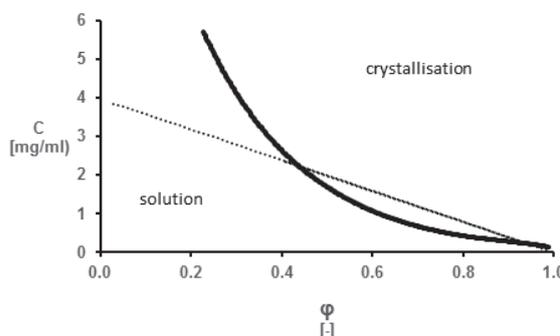
These differences indicated that for a 1 mg/ml solution, the supersaturation for crystallization is much larger than for a 0.5 mg/ml solution. All these results led ter Horst *et al* to investigate the phase behavior of lorazepam in mixed solutions.

The authors determined the solid-liquid phase diagram for commercially available lorazepam in mixtures with aqueous glucose solution by performing simple solubility measurements on the

**Crystal16** instrument. Known volumes of a commercially available lorazepam solution and a glucose solution in water were added to prepare 1 ml of a lorazepam crystal suspensions with known overall compositions. The **Crystal16** combines automation with integrated turbidity measurement to determine clear and cloud points resulting in solubility data and the generation of solubility curves in short time. The solubility diagram was constructed as a function of the volume fraction of glucose solution added when preparing the solution. The phase diagram showed that high lorazepam concentrations (low glucose solution volume fractions) leads to a stable solution in which no lorazepam crystallization will occur. This confirmed that the glucose solution acts as an anti-solvent, greatly reducing the lorazepam solubility in the infusion solution.



Measured saturation temperatures as a function of lorazepam concentration



Isothermal solubility diagram of lorazepam at 18°C

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